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Codon 219 Polymorphism of PRNP in Healthy Caucasians and Creutzfeldt-Jakob Disease Patients

To the Editor:

A number of point and insert mutations of the PrP gene (PRNP) have been linked to familial Creutzfeldt-Jakob disease (CJD) and Gerstmann-Sträussler-Scheinker disease (GSS) (for a review, see Pocchiari 1994; Goldfarb and Brown 1995). Moreover, the methionine/valine homozygosity at the polymorphic codon 129 of PRNP may cause a predisposition to sporadic (Palmer et al. 1991; Salvatore et al. 1994) and iatrogenic (Collinge et al. 1991; Brown et al. 1994) CJD or may control the age at onset of familial cases carrying either the 144-bp insertion (Poulter et al. 1992) or codon 178 (Goldfarb et al. 1992), codon 198 (Hsiao et al. 1989), and codon 210 (Pocchiari et al. 1993) pathogenic mutations in PRNP. In addition, the association of methionine or valine at codon 129 and the point mutation at codon 178 on the same allele seem to play an important role in determining either fatal familial insomnia or CJD (Goldfarb et al. 1992). However, it is noteworthy that a relationship between codon 129 polymorphism and accelerated pathogenesis (early age at onset or shorter duration of the disease) has not been seen in familial CJD patients with codon 200 mutation (Gabizon et al. 1993) or in GSS patients with codon 102 mutation (Barbanti et al. 1994; Hainfellner et al. 1995), arguing that other, as yet unidentified, gene products or environmental factors, or both, may influence the clinical expression of these diseases.

Recently, Furukawa et al. (1995) found a new G→A polymorphism in the first position of codon 219 of PRNP in 12 of 100 healthy Japanese people, with an allele frequency of 6%. This polymorphism results in the substitution of the most common negatively charged glutamic acid by the positively charged lysine. They also reported one GSS family whose affected members carried the GSS-related codon 102 mutation and the polymorphic lysine at codon 219 on the same allele. The authors stated that the clinicopathological features of these patients clearly differ from those of previously reported GSS patients with codon 102 mutation (Furukawa et al. 1995). These findings prompted us to analyze this polymorphism in our control and CJD Caucasian populations.

To determine the incidence of codon 219 polymorphism, we screened DNA samples of the following: 100 randomly selected unrelated healthy adult individuals of both sexes, collected from all over Italy; 59 sporadic CJD patients with no known PRNP mutation (in 36 patients the clinical diagnosis was confirmed by neuropathological examination and/or western blot detection of the disease-specific, partially protease-resistant, prion protein); 8 familial CJD patients with codon 210 mutation; 2 familial CJD patients with codon 200 mutation; and 1 GSS patient with codon 102 mutation. We also screened 34 healthy members (mutated and nonmutated individuals) of these families.

DNA was extracted from blood, according to standard procedures. Since the substitution of G by A in the first position of codon 219 of PRNP (Glu→Lys) does not create or abolish any restriction site, the restriction site–generated PCR was used to screen for the presence of this polymorphism. A mismatched sense primer (Sc-7) containing a C→A change at nucleotide 650 and a matched antisense primer (Sc-4) were prepared as described elsewhere (Furukawa et al. 1995). This substitution creates a restriction site for BsiW I (98 and 20 bp, respectively) in the PCR product (118 bp) only when the G nucleotide is present in the first position of codon 219. The accuracy of the test was assessed by using DNA samples whose entire open reading frames of PRNP were fully sequenced (Pocchiari et al. 1993; Barbanti et al. 1994).

All 100 Italian controls had Glu/Glu at codon 219, with a Glu:Lys allele frequency of 1:0, significantly different from that in the Japanese population (.94:.06; $P = .004$, Fisher exact test; Furukawa et al. 1995). Moreover, none of the 59 sporadic CJD patients, 11 familial CJD/GSS patients, or 34 healthy members of these families showed the polymorphic lysine at codon 219.

This discrepancy may be related to ethnic background. However, the finding that the Japanese and Caucasian populations have different gene frequencies at the polymorphic codons 219 and 129 (Owen et al. 1990; Doh-ura et al. 1991) may be highly relevant in the clinicopathological phenotype of CJD and related disorders. This is supported by the different influence

that the polymorphism at codon 129 has on clinical and pathological expression in Japanese (Miyazono et al. 1992) and Caucasian CJD patients (Salvatore et al. 1994).

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CFTR Gene Variant IVS8-5T in Disseminated Bronchiectasis

To the Editor:

Obstructive pulmonary disease includes asthma, chronic obstructive pulmonary disease (COPD; i.e., pulmonary emphysema and chronic bronchitis), bronchiectasis, and cystic fibrosis (CF) (Nadel 1994). It represents a leading cause of death in developed countries. Both familial clustering of non-CF obstructive pulmonary disease and familial aggregation of impaired lung function have been described (Kueppers 1992). This suggests that genetic factors contribute to non-CF obstructive pulmonary disease, even if it is difficult to determine the relative contribution of environmental factors.

Some clinical commonalities between CF and other obstructive pulmonary disease have been observed (Welsh et al. 1995); therefore the CF gene may be a candidate locus for a role in the etiology or the patho-